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FILE 'HOME' ENTERED AT 11:42:10 ON 22 SEP 2008

=> file react

=> d l1
L1 HAS NO ANSWERS
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*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

Structure attributes must be viewed using STN Express query preparation.


=> s l1 full
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SEARCH TIME: 00.00.02

FULL SEARCH INITIATED 11:43:07 FILE 'CHEMINFORMRX'
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SEARCH TIME: 00.00.01

L3           7 L1

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L3   ANSWER 1 OF 7  CASREACT  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:       144:274145  CASREACT
TITLE:                  Preparation of aryl and heteroaryl compounds having
                        β2 adrenergic receptor agonist and muscarinic
                        receptor antagonist activity
```

INVENTOR(S): Mammen, Mathai; Mischki, Trevor
PATENT ASSIGNEE(S): Theravance, Inc., USA
SOURCE: PCT Int. Appl., 125 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006023457	A1	20060302	WO 2005-US29018	20050815
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20060116398	A1	20060601	US 2005-204066	20050815
EP 1778626	A1	20070502	EP 2005-785444	20050815
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JP 2008510014	T	20080403	JP 2007-527920	20050815
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			WO 2005-US29018	20050815

OTHER SOURCE(S): MARPAT 144:274145
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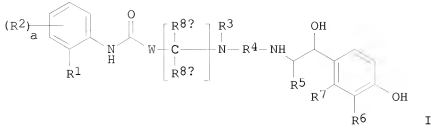

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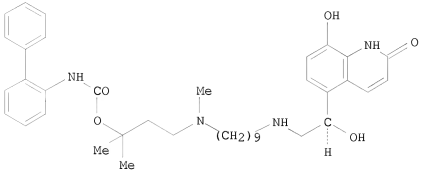
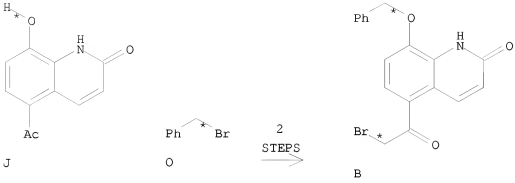


II

AB This invention provides compds. of formula I (wherein W = O or NWa; Wa = H or C1-4 alkyl; R1 = (un)substituted C6-10 aryl, C2-9 heteroaryl; R2 = C1-4 alkyl, C2-4 alkenyl, C3-6 cycloalkyl. etc.;R3 = H, (un)substituted C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, or C3-6 cycloalkyl; R4= a divalent hydrocarbon containing 4-28 carbons and optionally from 1-10 heteroatoms; R5 = H or C1-4 alkyl; R6 = N(R6a)C(O)R6b or CR6cR6dOR6e ; and R7 = H; or R6 and R7 together form N(R7a)C(O)C(R7b)=C(R7c), etc., where R6a-R6e and R7a-R7c = H or C1-4alkyl; R8a and R8b = H, C1-4 alkyl, OH, F, or R8a and R8b are part of a C3-6 cycloalkylene ring or a C2-5 heterocyclene ring; a = 0-3; b= 2-8) or a pharmaceutically acceptable salt or solvate or stereoisomer thereof. The compds. of this invention possess both β2 adrenergic receptor agonist and muscarinic receptor antagonist activity. Accordingly, such compds. are expected to be useful as therapeutic agents for treating pulmonary disorders, such as chronic obstructive pulmonary disease and asthma. For example, II was prepared from biphenyl-2-ylcarbamic acid 3-[(9-hydroxynonyl)methylamino]-1,1-dimethylpropyl ester (preparation given) and 5-[(R)-2-amino-1-(tert-butyldimethylsilanyloxy)ethyl]-8-hydroxy-1H-quinolin-2-one acetic acid salt (preparation given); II had a Ki of <300 nM in a radioligand binding assay for human β2 receptors and for M3 muscarinic receptor.

RX(46) OF 417 COMPOSED OF RX(4), RX(1)
RX(46) J + O ===> B



RX(4) RCT J 62978-73-8, O 100-39-0

STAGE(1)
RGT P 584-08-7 K2CO3
SOL 68-12-2 DMF
CON 2.25 hours, room temperature

STAGE(2)
RGT Q 7647-14-5 NaCl
SOL 7732-18-5 Water
CON 1 hour, 0 deg C

PRO A 93609-84-8

RX(1) RCT A 93609-84-8

STAGE(1)
RGT C 109-63-7 BF3-Et2O
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) room temperature -> 0 deg C
SUBSTAGE(2) 0 deg C
SUBSTAGE(3) 0 deg C -> room temperature
SUBSTAGE(4) 45 deg C

STAGE(2)
RGT D 7726-95-6 Br2
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) 40 minutes, 45 deg C
SUBSTAGE(2) 15 minutes, 45 deg C
SUBSTAGE(3) 45 deg C -> room temperature

PRO B 100331-89-3
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 144:88180 CASREACT
TITLE: Method for preparing 8-substituted oxy-5-((R)-2-halo-1-hydroxy-ethyl)-(1

H)-quinolin-2-ones employing a chiral reduction step

INVENTOR(S): Lohse, Olivier; Vogel, Caspar; Abel, Stephan
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis Pharma GmbH
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005123684	A2	20051229	WO 2005-EP6686	20050621
WO 2005123684	A3	20060601		
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AU 2005254698	A1	20051229	AU 2005-254698	20050621
CA 2566388	A1	20051229	CA 2005-2566388	20050621
CN 1968927	A	20070523	CN 2005-80019589	20050621
EP 1791820	A2	20070606	EP 2005-770221	20050621
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BR 2005012298	A	20080325	BR 2005-12298	20050621
IN 2006DN06563	A	20070831	IN 2006-DN6563	20061106
MX 2006PA14695	A	20070212	MX 2006-PA14695	20061214
KR 2007029752	A	20070314	KR 2006-726958	20061221
NO 2007000400	A	20070321	NO 2007-400	20070122
PRIORITY APPLN. INFO.:			GB 2004-13960	20040622
			WO 2005-EP6686	20050621

OTHER SOURCE(S): MARPAT 144:88180
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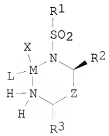
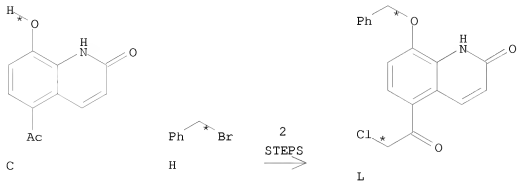


I

AB A process for preparing 8-substituted oxy-5-((R)-2-halo-1-hydroxy-ethyl)-(1 H)-quinolin-2-ones or acceptable solvates thereof which are useful intermediates from which to prepare 5-[(R)-2-(5,6-diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-(1H)-quinolin-2-one salts. The process involves reacting a 5-(α-haloacetyl)-8-substituted oxy-(1H)-quinolin-2-one with a reducing agent in the presence of a chiral agent and a base to form a 8-(substituted oxy)-5-((R)-2-halo-1-hydroxy-ethyl)-(1H)-quinolin-2-one, said chiral agent having a formula I [wherein M = Ru, Rh, Ir, Fe, Co, or Ni; L = aryl or arylalkyl; X = H or halo; R1 = alkyl, cycloalkyl, aryl, etc.; R2 and R3 = Ph or together form a cyclohexane or cyclopentane ring; Z = bond or 1,1'-ferrocenediyl].

RX(19) OF 73 COMPOSED OF RX(3), RX(4)
RX(19) C + H ===> L



RX(3) RCT C 62978-73-8

STAGE(1)
RGT J 7087-68-5 EtN(Pr-i)2
SOL 7732-18-5 Water, 67-64-1 Me2CO
CON room temperature -> reflux

STAGE(2)
RCT H 100-39-0
CON SUBSTAGE(1) reflux
SUBSTAGE(2) 6 - 7 hours, reflux

STAGE(3)
RGT E 7732-18-5 Water
CON SUBSTAGE(1) 58 deg C
SUBSTAGE(2) 58 deg C -> 25 deg C

PRO I 93609-84-8

RX(4) RCT I 93609-84-8

STAGE(1)
RGT M 114971-52-7 Me3NCH2Ph.Cl2I
SOL 64-19-7 AcOH
CON SUBSTAGE(1) 65 - 70 deg C

SUBSTAGE(2) 70 deg C -> 45 deg C
SUBSTAGE(3) 30 - 60 minutes, 40 - 45 deg C

STAGE(2)
RGT E 7732-18-5 Water
CON 30 - 60 minutes, 20 - 25 deg C

STAGE(3)
RGT N 7631-90-5 NaHSO3
SOL 7732-18-5 Water
CON 30 - 60 minutes, 15 - 20 deg C

PRO L 63404-86-4

L3 ANSWER 3 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 141:410823 CASREACT
TITLE: Preparation and formulation of crystalline forms of a quinolinone β2 adrenergic receptor agonist for treatment of pulmonary disease
INVENTOR(S): Axt, Sabine; Stergiades, Ioanna
PATENT ASSIGNEE(S): Theravance, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 20 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20040224982	A1	20041111	US 2004-841761	20040507
US 7060712	B2	20060613		
WO 2004101525	A1	20041125	WO 2004-US14302	20040507
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1622875	A1	20060208	EP 2004-751604	20040507
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JP 2006528242	T	20061214	JP 2006-532854	20040507
PRIORITY APPLN. INFO.:			US 2003-468810P	20030508
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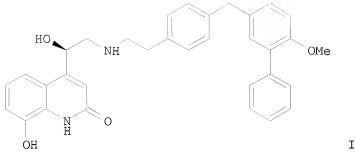
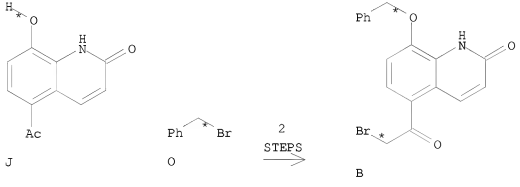


I

AB The invention provides crystalline solvate forms of a salt of a novel β2 adrenergic receptor agonist, 8-hydroxy-5-[(R)-1-hydroxy-2-[[2-[4-[(6-methoxybiphenyl-3-yl)amino]phenyl]ethyl]amino]ethyl]-1H-quinolin-2-one (I). The invention also provides pharmaceutical compns. comprising the solvate forms, formulations containing the pharmaceutical compns., methods of using the solvate forms to treat pulmonary disease, and processes useful for preparing such solvate forms. For example, I•HCl was synthesized in six steps starting from 5-(2-bromo-1-oxoethyl)-8-benzyloxy-2(1H)-quinolinone, 4-bromophenethylamine, and 4-methoxy-3-phenylaniline•HCl. Two solvated crystalline forms of I•HCl, a water/isopropanol solvate and a hydrate, were formed and characterized by x-ray powder diffraction pattern anal., differential scanning calorimetry, thermogravimetric anal., IR, NMR, HPLC, mass spectrometry, elemental anal., GC, and inductively coupled plasma spectroscopy.

RX(15) OF 65 COMPOSED OF RX(4), RX(1)
RX(15) J + O ===> B



J B

RX(4) RCT J 62978-73-8, O 100-39-0

STAGE(1)
RGT P 584-08-7 K2CO3
SOL 68-12-2 DMF
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 2.25 hours, room temperature

```
            STAGE(2)
               RGT  Q 7647-14-5 NaCl
               SOL  7732-18-5 Water
               CON  SUBSTAGE(2) 1 hour

          PRO  A 93609-84-8

RX(1)     RCT  A 93609-84-8

            STAGE(1)
               RGT  C 109-63-7 BF3-Et2O
               SOL  75-09-2 CH2Cl2
               CON  SUBSTAGE(1) room temperature -> 0 deg C
                    SUBSTAGE(3) room temperature
                    SUBSTAGE(4) 45 deg C

            STAGE(2)
               RGT  D 7726-95-6 Br2
               SOL  75-09-2 CH2Cl2
               CON  SUBSTAGE(1) 40 minutes, 45 deg C
                    SUBSTAGE(2) 15 minutes, 45 deg C

          PRO  B 100331-89-3
REFERENCE COUNT:         16    THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


L3   ANSWER 4 OF 7  CASREACT  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        141:225161  CASREACT
TITLE:                   Preparation of biphenyl derivatives as
                         β2-adrenergic agonists and muscarinic antagonists
                         for pulmonary disorders.
INVENTOR(S):             Mammen, Mathai; Dunham, Sarah; Hughes, Adam; Lee, Tae
                         Weon; Husfeld, Craig; Stangeland, Eric
PATENT ASSIGNEE(S):      Theravance, Inc., USA
SOURCE:                  U.S. Pat. Appl. Publ., 85 pp.
                         CODEN: USXXCO
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

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     US 20040167167    A1   20040826      US 2004-779157   20040213
     US 7141671        B2   20061128
     AU 2004213411     A1   20040902      AU 2004-213411   20040213
     CA 2515777        A1   20040902      CA 2004-2515777  20040213
     WO 2004074276     A1   20040902      WO 2004-US4224   20040213
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             MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
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WO 2004074812 A3 20041104
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CN 101239970 A 20080813 CN 2008-10074159 20040213
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US 20060223859 A1 20061005 US 2006-448294 20060607
US 7355046 B2 20080408
US 20060223860 A1 20061005 US 2006-448317 20060607
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US 20070037984 A1 20070215 US 2006-582885 20061018
US 20070088054 A1 20070419 US 2006-604607 20061127
JP 2007119496 A 20070517 JP 2007-31325 20070209
US 20070208176 A1 20070906 US 2007-788343 20070419
US 20070276003 A1 20071129 US 2007-879004 20070713
US 20080015220 A1 20080117 US 2007-888526 20070801
PRIORITY APPLN. INFO.: US 2003-447843P 20030214

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	JP 2006-503604	20040213
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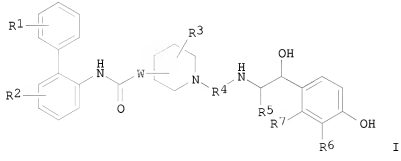
	WO 2004-US4224	20040213
	WO 2004-US4273	20040213
	WO 2004-US4449	20040213
	US 2006-448293	20060607
	US 2006-448294	20060607

OTHER SOURCE(S): MARPAT 141:225161

GI



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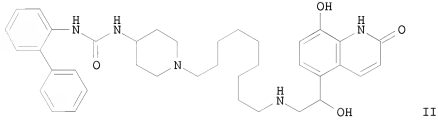
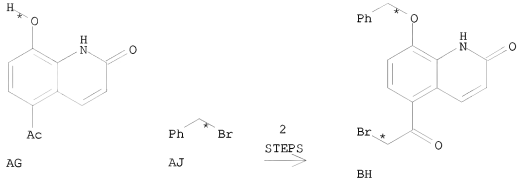


II

AB Title compds. I [R1 (taken 0-3 times) = alk(en/yn)yl, cycloalkyl, etc.; R2 (taken 0-3 times) = alk(en/yn)yl, cycloalkyl, CN, etc.; W = O, substituted N; R3 (taken 0-4 times) = alk(en/yn)yl, cycloalkyl, etc.; R4 = divalent group; R5 = H, alkyl; R6 = amino, alkoxy, etc.; R7 = H, etc.] are prepared For instance, N-[1,1'-Biphenyl-2-yl]-N'-[1-(9-amininonyl)piperidin-4-yl]urea (preparation given) is combined with 8-Benzyloxy-5-(2,2-dihydroxyacetyl)-1H-quinolin-2-one (CH2Cl2, NaHB(OAc)3) and the product reduced (MeOH, H2-Pd/C) to give II. Selected example compds. have Ki < 10 nM for the β2 and muscarinic receptor. I are useful in the treatment of pulmonary disorders, such as chronic obstructive pulmonary disease and asthma.

RX(173) OF 1000 COMPOSED OF RX(10), RX(20)

RX(173) AG + AJ ===> BH



RX(10) RCT AG 62978-73-8, AJ 100-39-0

STAGE(1)
RGT AK 584-08-7 K2CO3
SOL 68-12-2 DMF
CON 2.25 hours, room temperature

STAGE(2)
RGT AL 7647-14-5 NaCl
SOL 7732-18-5 Water
CON 1 hour, 0 deg C

PRO Y 93609-84-8

RX(20) RCT Y 93609-84-8

STAGE(1)
RGT BI 109-63-7 BF3-Et2O
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) room temperature -> 0 deg C
SUBSTAGE(2) 0 deg C
SUBSTAGE(3) 0 deg C -> room temperature
SUBSTAGE(4) 45 deg C

STAGE(2)
RGT BJ 7726-95-6 Br2
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) 40 minutes, 45 deg C
SUBSTAGE(2) 15 minutes, 45 deg C
SUBSTAGE(3) 45 deg C -> room temperature

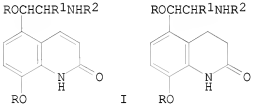
PRO BH 100331-89-3
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 103:6245 CASREACT
TITLE: Carbostyril derivatives

PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

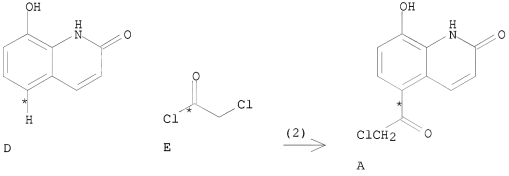
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 60023365	A	19850205	JP 1984-63707	19840330
JP 60059913	B	19851227		

PRIORITY APPLN. INFO.: JP 1984-63707 19840330
GI



AB Title compds. I and II (R = acyl; R1, R2 = H, alkyl) and their salts were prepared Thus, treating 1 g I HCl (R = H, R1 = Et, R2 = Me2CH) with 10 mL isobutyryl anhydride in the presence of concentrated H2SO4 gave 0.75 g I (R isobutyryl, R1 = Et, R2 = Me2CH). I HCl (R = Ac, R1 = Et, R2 = Me2CH) showed bronchodilator activity in dogs.

RX(2) OF 6 D + E ===> A...



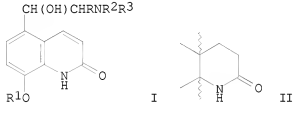
RX(2) RCT D 15450-76-7, E 79-04-9
PRO A 56957-71-2

L3 ANSWER 6 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 102:45790 CASREACT
TITLE: Carbostyril derivatives

PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

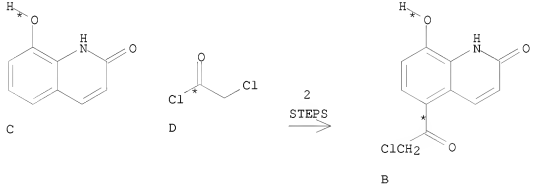
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 59093051	A	19840529	JP 1983-204602	19831031
JP 60010032	B	19850314		
PRIORITY APPLN. INFO.:			JP 1983-204602	19831031

GI



AB Seventeen carbostyril derivs. I (R = H, alkyl; R1 = H, Me, Me2CHCO; R2, R3 = H, alkyl, cycloalkyl; R2R3N may form a piperidino, pyrrolidino, piperazino, or morpholino group) were prepared by dehydrogenation of II. I had anticholesteremic, vasodilating, diuretic, etc., activities (no data). Thus, refluxing 2.2 g II (R = R1 = R2 = R3 = H) with 2.5 g chloranil in xylene 24 h gave 1.5 g I.HCl (R = R1 = R2 = R3 = H).

RX(4) OF 4 COMPOSED OF RX(2), RX(1)
RX(4) C + D ===> B



RX(2) RCT C 15450-76-7, D 79-04-9
PRO A 57275-84-0

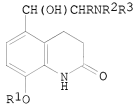
RX(1) RCT A 57275-84-0

PRO B 56957-71-2

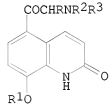
L3 ANSWER 7 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 101:191719 CASREACT
TITLE: 3,4-Dihydrocarbostyril derivatives
PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 59093053	A	19840529	JP 1983-204604	19831031
JP 60010034	B	19850314		

PRIORITY APPLN. INFO.: JP 1983-204604 19831031
GI



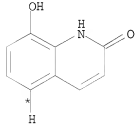
I



II

AB 3,4-Dihydrocarbostyril derivs. I [R, R1, R2, R3 = H, H, H, PhCMe2CH2 (HCl); H, Me, H, Me2CH (HCl); Et, H, H, PhCH2CH2 (HCl); H, H, H, cyclohexyl (HBr); H, Me, H, Me2CH (HCl); Et, Me2CHCO, H, Me2CH (HCl)] were prepared by reduction of II. I had immunosuppressive, antiallergic, and antiviral activities (no data). Thus, autoclaving a mixture of 1 g II.HCl (R = R1 = R2 = H, R3 = PhCMe2CH2), 0.2 g PtO2, 50 mL H2O, and 5 atm H at 80° for 20 h gave 0.8 g I.HCl (R = R1 = R2 = H, R3 = PhCMe2CH2).

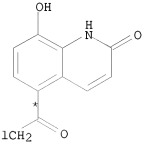
RX(1) OF 2 A + B ===> C



A

B

(1)



C

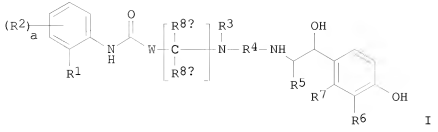
RX(1) RCT A 15450-76-7, B 79-04-9
PRO C 56957-71-2

=> d ibib abs rx 1-7

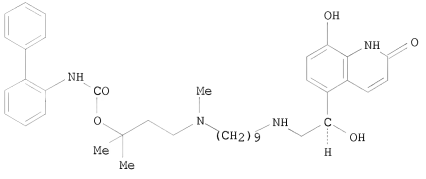
L3 ANSWER 1 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 144:274145 CASREACT
TITLE: Preparation of aryl and heteroaryl compounds having β2 adrenergic receptor agonist and muscarinic receptor antagonist activity
INVENTOR(S): Mammen, Mathai; Mischki, Trevor
PATENT ASSIGNEE(S): Theravance, Inc., USA
SOURCE: PCT Int. Appl., 125 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006023457	A1	20060302	WO 2005-US29018	20050815
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20060116398	A1	20060601	US 2005-204066	20050815
EP 1778626	A1	20070502	EP 2005-785444	20050815
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, HR				
JP 2008510014	T	20080403	JP 2007-527920	20050815
PRIORITY APPLN. INFO.:			US 2004-601781P	20040816
			WO 2005-US29018	20050815

OTHER SOURCE(S): MARPAT 144:274145
GI



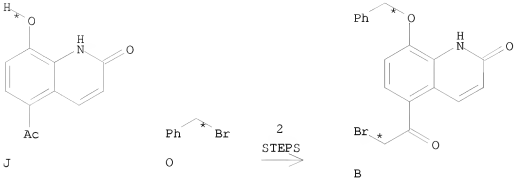
I



II

AB This invention provides compds. of formula I (wherein W = O or NWa; Wa = H or C1-4 alkyl; R1 = (un)substituted C6-10 aryl, C2-9 heteroaryl; R2 = C1-4 alkyl, C2-4 alkenyl, C3-6 cycloalkyl. etc.;R3 = H, (un)substituted C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, or C3-6 cycloalkyl; R4= a divalent hydrocarbon containing 4-28 carbons and optionally from 1-10 heteroatoms; R5 = H or C1-4 alkyl; R6 = N(R6a)C(O)R6b or CR6cR6dOR6e ; and R7 = H; or R6 and R7 together form N(R7a)C(O)C(R7b)=C(R7c), etc., where R6a-R6e and R7a-R7c = H or C1-4alkyl; R8a and R8b = H, C1-4 alkyl, OH, F, or R8a and R8b are part of a C3-6 cycloalkylene ring or a C2-5 heterocyclene ring; a = 0-3; b= 2-8) or a pharmaceutically acceptable salt or solvate or stereoisomer thereof. The compds. of this invention possess both β2 adrenergic receptor agonist and muscarinic receptor antagonist activity. Accordingly, such compds. are expected to be useful as therapeutic agents for treating pulmonary disorders, such as chronic obstructive pulmonary disease and asthma. For example, II was prepared from biphenyl-2-ylcarbamic acid 3-[(9-hydroxynonyl)methylamino]-1,1-dimethylpropyl ester (preparation given) and 5-[(R)-2-amino-1-(tert-butyldimethylsilanyloxy)ethyl]-8-hydroxy-1H-quinolin-2-one acetic acid salt (preparation given); II had a Ki of <300 nM in a radioligand binding assay for human β2 receptors and for M3 muscarinic receptor.

RX(46) OF 417 COMPOSED OF RX(4), RX(1)
RX(46) J + O ===> B



RX(4) RCT J 62978-73-8, O 100-39-0

STAGE(1)
RGT P 584-08-7 K2CO3
SOL 68-12-2 DMF
CON 2.25 hours, room temperature

STAGE(2)
RGT Q 7647-14-5 NaCl
SOL 7732-18-5 Water
CON 1 hour, 0 deg C

PRO A 93609-84-8

RX(1) RCT A 93609-84-8

STAGE(1)
RGT C 109-63-7 BF3-Et2O
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) room temperature -> 0 deg C
SUBSTAGE(2) 0 deg C
SUBSTAGE(3) 0 deg C -> room temperature
SUBSTAGE(4) 45 deg C

STAGE(2)
RGT D 7726-95-6 Br2
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) 40 minutes, 45 deg C
SUBSTAGE(2) 15 minutes, 45 deg C
SUBSTAGE(3) 45 deg C -> room temperature

PRO B 100331-89-3

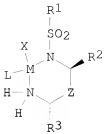
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 7 CASREACT COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 144:88180 CASREACT
TITLE: Method for preparing 8-substituted oxy-5-((R)-2-halo-1-hydroxy-ethyl)-(1H)-quinolin-2-ones employing a chiral reduction step
INVENTOR(S): Lohse, Olivier; Vogel, Caspar; Abel, Stephan
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis Pharma GmbH
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005123684	A2	20051229	WO 2005-EP6686	20050621
WO 2005123684	A3	20060601		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2005254698	A1	20051229	AU 2005-254698	20050621
CA 2566388	A1	20051229	CA 2005-2566388	20050621
CN 1968927	A	20070523	CN 2005-80019589	20050621
EP 1791820	A2	20070606	EP 2005-770221	20050621
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU				
JP 2008503526	T	20080207	JP 2007-517180	20050621
BR 2005012298	A	20080325	BR 2005-12298	20050621
IN 2006DN06563	A	20070831	IN 2006-DN6563	20061106
MX 2006PA14695	A	20070212	MX 2006-PA14695	20061214
KR 2007029752	A	20070314	KR 2006-726958	20061221
NO 2007000400	A	20070321	NO 2007-400	20070122
PRIORITY APPLN. INFO.:			GB 2004-13960	20040622
			WO 2005-EP6686	20050621

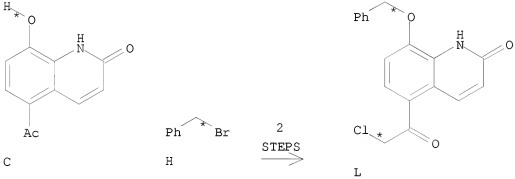
OTHER SOURCE(S): MARPAT 144:88180
GI



I

AB A process for preparing 8-substituted oxy-5-((R)-2-halo-1-hydroxy-ethyl)-(1 H)-quinolin-2-ones or acceptable solvates thereof which are useful intermediates from which to prepare 5-[(R)-2-(5,6-diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-(1H)-quinolin-2-one salts. The process involves reacting a 5-(α-haloacetyl)-8-substituted oxy-(1H)-quinolin-2-one with a reducing agent in the presence of a chiral agent and a base to form a 8-(substituted oxy)-5-((R)-2-halo-1-hydroxy-ethyl)-(1H)-quinolin-2-one, said chiral agent having a formula I [wherein M = Ru, Rh, Ir, Fe, Co, or Ni; L = aryl or arylalkyl; X = H or halo; R1 = alkyl, cycloalkyl, aryl, etc.; R2 and R3 = Ph or together form a cyclohexane or cyclopentane ring; Z = bond or 1,1'-ferrocenediyl].

RX(19) OF 73 COMPOSED OF RX(3), RX(4)
RX(19) C + H ===> L



C H L

RX(3) RCT C 62978-73-8

STAGE(1)
RGT J 7087-68-5 EtN(Pr-i)2
SOL 7732-18-5 Water, 67-64-1 Me2CO
CON room temperature -> reflux

STAGE(2)
RCT H 100-39-0
CON SUBSTAGE(1) reflux
SUBSTAGE(2) 6 - 7 hours, reflux

```
            STAGE(3)
               RGT  E 7732-18-5 Water
               CON  SUBSTAGE(1) 58 deg C
                    SUBSTAGE(2) 58 deg C -> 25 deg C

          PRO  I 93609-84-8

RX(4)     RCT  I 93609-84-8

            STAGE(1)
               RGT  M 114971-52-7 Me3NCH2Ph.Cl2I
               SOL  64-19-7 AcOH
               CON  SUBSTAGE(1) 65 - 70 deg C
                    SUBSTAGE(2) 70 deg C -> 45 deg C
                    SUBSTAGE(3) 30 - 60 minutes, 40 - 45 deg C

            STAGE(2)
               RGT  E 7732-18-5 Water
               CON  30 - 60 minutes, 20 - 25 deg C

            STAGE(3)
               RGT  N 7631-90-5 NaHSO3
               SOL  7732-18-5 Water
               CON  30 - 60 minutes, 15 - 20 deg C

          PRO  L 63404-86-4


RX(29) OF 73 COMPOSED OF RX(1), RX(3), RX(4)
RX(29)    A  +  B  +  H  ===>  L
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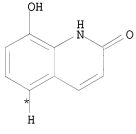
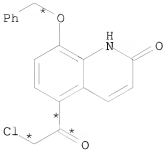


A

B

H



L

RX(1) RCT A 15450-76-7

STAGE(1)
RGT D 7446-70-0 AlCl3
SOL 95-50-1 o-C6H4Cl2
CON 40 minutes, 20 - 25 deg C

STAGE(2)
RCT B 108-24-7
SOL 95-50-1 o-C6H4Cl2
CON SUBSTAGE(1) 30 minutes, 20 deg C
SUBSTAGE(2) 30 minutes, 20 - 25 deg C
SUBSTAGE(3) 25 deg C -> 80 deg C
SUBSTAGE(4) 1 hour, 80 deg C

STAGE(3)
RGT E 7732-18-5 Water
CON SUBSTAGE(1) 80 deg C
SUBSTAGE(2) 15 minutes, reflux
SUBSTAGE(3) 15 minutes, 80 deg C

PRO C 62978-73-8
NTE regioselective, optimization study, optimized on stoichiometry

RX(3) RCT C 62978-73-8

STAGE(1)
RGT J 7087-68-5 EtN(Pr-i)2
SOL 7732-18-5 Water, 67-64-1 Me2CO
CON room temperature -> reflux

STAGE(2)
RCT H 100-39-0
CON SUBSTAGE(1) reflux
SUBSTAGE(2) 6 - 7 hours, reflux

STAGE(3)
RGT E 7732-18-5 Water
CON SUBSTAGE(1) 58 deg C
SUBSTAGE(2) 58 deg C -> 25 deg C

PRO I 93609-84-8

RX(4) RCT I 93609-84-8

STAGE(1)
RGT M 114971-52-7 Me3NCH2Ph.C12I
SOL 64-19-7 AcOH
CON SUBSTAGE(1) 65 - 70 deg C
SUBSTAGE(2) 70 deg C -> 45 deg C
SUBSTAGE(3) 30 - 60 minutes, 40 - 45 deg C

STAGE(2)
RGT E 7732-18-5 Water
CON 30 - 60 minutes, 20 - 25 deg C

STAGE(3)
RGT N 7631-90-5 NaHSO3
SOL 7732-18-5 Water
CON 30 - 60 minutes, 15 - 20 deg C

PRO L 63404-86-4

L3 ANSWER 3 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 141:410823 CASREACT
TITLE: Preparation and formulation of crystalline forms of a quinolinone β2 adrenergic receptor agonist for treatment of pulmonary disease
INVENTOR(S): Axt, Sabine; Stergiades, Ioanna
PATENT ASSIGNEE(S): Theravance, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 20 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20040224982	A1	20041111	US 2004-841761	20040507
US 7060712	B2	20060613		
WO 2004101525	A1	20041125	WO 2004-US14302	20040507

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1622875 A1 20060208 EP 2004-751604 20040507
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK
JP 2006528242 T 20061214 JP 2006-532854 20040507
PRIORITY APPLN. INFO.: US 2003-468810P 20030508
WO 2004-US14302 20040507

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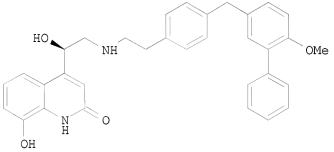
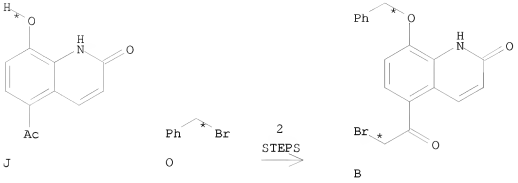


I

AB The invention provides crystalline solvate forms of a salt of a novel β2 adrenergic receptor agonist, 8-hydroxy-5-[(R)-1-hydroxy-2-[[2-[4-[(6-methoxybiphenyl-3-yl)amino]phenyl]ethyl]amino]ethyl]-1H-quinolin-2-one (I). The invention also provides pharmaceutical compns. comprising the solvate forms, formulations containing the pharmaceutical compns., methods of using the solvate forms to treat pulmonary disease, and processes useful for preparing such solvate forms. For example, I•HCl was synthesized in six steps starting from 5-(2-bromo-1-oxoethyl)-8-benzyloxy-2(1H)-quinolinone, 4-bromophenethylamine, and 4-methoxy-3-phenylaniline•HCl. Two solvated crystalline forms of I•HCl, a water/isopropanol solvate and a hydrate, were formed and characterized by x-ray powder diffraction pattern anal., differential scanning calorimetry, thermogravimetric anal., IR, NMR, HPLC, mass spectrometry, elemental anal., GC, and inductively coupled plasma spectroscopy.

RX(15) OF 65 COMPOSED OF RX(4), RX(1)
RX(15) J + O ===> B



RX(4) RCT J 62978-73-8, O 100-39-0

STAGE(1)
RGT P 584-08-7 K2CO3
SOL 68-12-2 DMF
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 2.25 hours, room temperature

STAGE(2)
RGT Q 7647-14-5 NaCl
SOL 7732-18-5 Water
CON SUBSTAGE(2) 1 hour

PRO A 93609-84-8

RX(1) RCT A 93609-84-8

STAGE(1)
RGT C 109-63-7 BF3-Et2O
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) room temperature -> 0 deg C
SUBSTAGE(3) room temperature
SUBSTAGE(4) 45 deg C

STAGE(2)
RGT D 7726-95-6 Br2
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) 40 minutes, 45 deg C
SUBSTAGE(2) 15 minutes, 45 deg C

PRO B 100331-89-3

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 141:225161 CASREACT

TITLE: Preparation of biphenyl derivatives as β2-adrenergic agonists and muscarinic antagonists for pulmonary disorders.
INVENTOR(S): Mammen, Mathai; Dunham, Sarah; Hughes, Adam; Lee, Tae Weon; Husfeld, Craig; Stangeland, Eric
PATENT ASSIGNEE(S): Theravance, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 85 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20040167167	A1	20040826	US 2004-779157	20040213
US 7141671	B2	20061128		
AU 2004213411	A1	20040902	AU 2004-213411	20040213
CA 2515777	A1	20040902	CA 2004-2515777	20040213
WO 2004074276	A1	20040902	WO 2004-US4224	20040213
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WO 2004074812	A2	20040902	WO 2004-US4273	20040213
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US 20040209915	A1	20041021	US 2004-778290	20040213
US 20040209860	A1	20041021	US 2004-778649	20040213
EP 1592685	A1	20051109	EP 2004-711137	20040213
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EP 1594860	A2	20051116	EP 2004-711117	20040213
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EP 1615889	A2	20060118	EP 2004-711253	20040213

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BR	2004007508	A	20060214	BR 2004-7508	20040213
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JP	2006517978	T	20060803	JP 2006-503604	20040213
JP	2006518739	T	20060817	JP 2006-503553	20040213
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CN	101239968	A	20080813	CN 2008-10074156	20040213
CN	101239969	A	20080813	CN 2008-10074157	20040213
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CN	101239971	A	20080813	CN 2008-10074160	20040213
IN	2005DN03375	A	20070119	IN 2005-DN3375	20050728
ZA	2005006215	A	20060628	ZA 2005-6215	20050803
NO	2005004206	A	20051019	NO 2005-4206	20050909
US	20060223858	A1	20061005	US 2006-448293	20060607
US	7345175	B2	20080318		
US	20060223859	A1	20061005	US 2006-448294	20060607
US	7355046	B2	20080408		
US	20060223860	A1	20061005	US 2006-448317	20060607
US	20060229334	A1	20061012	US 2006-449004	20060607
US	20070037984	A1	20070215	US 2006-582885	20061018
US	20070088054	A1	20070419	US 2006-604607	20061127
JP	2007119496	A	20070517	JP 2007-31325	20070209
US	20070208176	A1	20070906	US 2007-788343	20070419
US	20070276003	A1	20071129	US 2007-879004	20070713
US	20080015220	A1	20080117	US 2007-888526	20070801

PRIORITY APPLN. INFO.:

US 2003-447843P	20030214
US 2003-467035P	20030501
CN 2004-80006528	20040213
JP 2006-503604	20040213
US 2004-779157	20040213
WO 2004-US4224	20040213
WO 2004-US4273	20040213
WO 2004-US4449	20040213
US 2006-448293	20060607
US 2006-448294	20060607

OTHER SOURCE(S): MARPAT 141:225161

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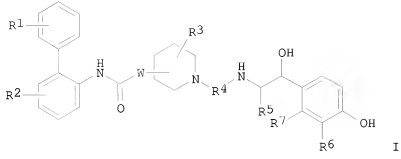

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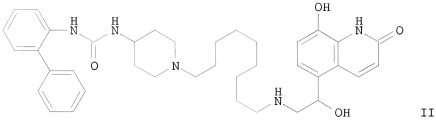
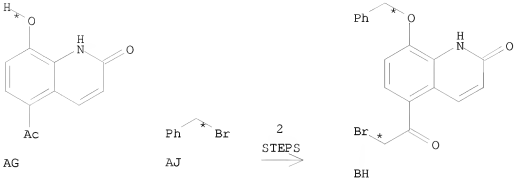


II

AB Title compds. I [R1 (taken 0-3 times) = alk(en/yn)yl, cycloalkyl, etc.; R2 (taken 0-3 times) = alk(en/yn)yl, cycloalkyl, CN, etc.; W = O, substituted N; R3 (taken 0-4 times) = alk(en/yn)yl, cycloalkyl, etc.; R4 = divalent group; R5 = H, alkyl; R6 = amino, alkoxy, etc.; R7 = H, etc.] are prepared For instance, N-[1,1'-Biphenyl-2-yl]-N'-[1-(9-aminononyl)piperidin-4-yl]urea (preparation given) is combined with 8-Benzyloxy-5-(2,2-dihydroxyacetyl)-1H-quinolin-2-one (CH_2Cl_2, $NaHB(OAc)_3$) and the product reduced (MeOH, H2-Pd/C) to give II. Selected example compds. have Ki < 10 nM for the β2 and muscarinic receptor. I are useful in the treatment of pulmonary disorders, such as chronic obstructive pulmonary disease and asthma.

RX(173) OF 1000 COMPOSED OF RX(10), RX(20)
RX(173) AG + AJ ===> BH



RX(10) RCT AG 62978-73-8, AJ 100-39-0

STAGE(1)
RGT AK 584-08-7 K2CO3
SOL 68-12-2 DMF
CON 2.25 hours, room temperature

STAGE(2)
RGT AL 7647-14-5 NaCl
SOL 7732-18-5 Water
CON 1 hour, 0 deg C

PRO Y 93609-84-8

RX(20) RCT Y 93609-84-8

STAGE(1)
RGT BI 109-63-7 BF3-Et2O
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) room temperature -> 0 deg C
SUBSTAGE(2) 0 deg C
SUBSTAGE(3) 0 deg C -> room temperature
SUBSTAGE(4) 45 deg C

STAGE(2)
RGT BJ 7726-95-6 Br2
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) 40 minutes, 45 deg C
SUBSTAGE(2) 15 minutes, 45 deg C
SUBSTAGE(3) 45 deg C -> room temperature

PRO BH 100331-89-3

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 7 CASREACT COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 103:6245 CASREACT
TITLE: Carbostyril derivatives
PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 60023365	A	19850205	JP 1984-63707	19840330
JP 60059913	B	19851227		
PRIORITY APPLN. INFO.:			JP 1984-63707	19840330

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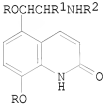

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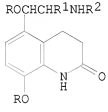
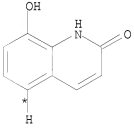


II

AB Title compds. I and II (R = acyl; R1, R2 = H, alkyl) and their salts were prepared Thus, treating 1 g I HCl (R = H, R1 = Et, R2 = Me2CH) with 10 mL isobutyryl anhydride in the presence of concentrated H2SO4 gave 0.75 g I (R isobutyryl, R1 = Et, R2 = Me2CH). I HCl (R = Ac, R1 = Et, R2 = Me2CH) showed bronchodilator activity in dogs.

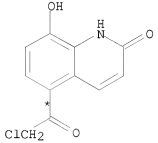
RX(2) OF 6 D + E ===> A...



D

E

(2)



A

RX(2) RCT D 15450-76-7, E 79-04-9
PRO A 56957-71-2

L3 ANSWER 6 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 102:45790 CASREACT
TITLE: Carbostyril derivatives
PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 59093051	A	19840529	JP 1983-204602	19831031
JP 60010032	B	19850314		
PRIORITY APPLN. INFO.:			JP 1983-204602	19831031

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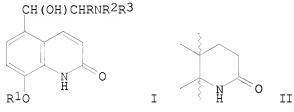
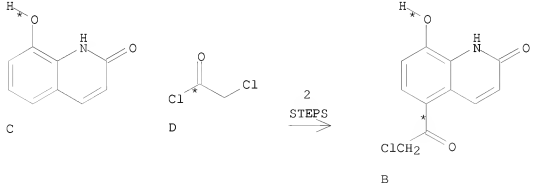


AB Seventeen carbostyril derivs. I (R = H, alkyl; R1 = H, Me, Me2CHCO; R2, R3 = H, alkyl, cycloalkyl; R2R3N may form a piperidino, pyrrolidino, piperazino, or morpholino group) were prepared by dehydrogenation of II. I had anticholesteremic, vasodilating, diuretic, etc., activities (no data). Thus, refluxing 2.2 g II (R = R1 = R2 = R3 = H) with 2.5 g chloranil in xylene 24 h gave 1.5 g I.HCl (R = R1 = R2 = R3 = H).

RX(4) OF 4 COMPOSED OF RX(2), RX(1)
RX(4) C + D ===> B



RX(2) RCT C 15450-76-7, D 79-04-9
PRO A 57275-84-0

RX(1) RCT A 57275-84-0
PRO B 56957-71-2

L3 ANSWER 7 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 101:191719 CASREACT
TITLE: 3,4-Dihydrocarbostyril derivatives
PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 59093053	A	19840529	JP 1983-204604	19831031
JP 60010034	B	19850314		
PRIORITY APPLN. INFO.:			JP 1983-204604	19831031

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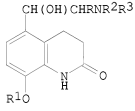

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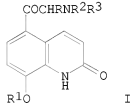
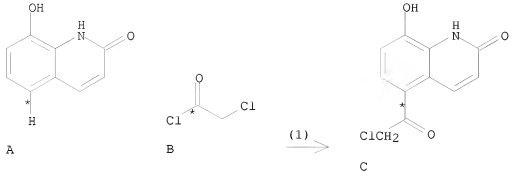


II

AB 3,4-Dihydrocarbostyril derivs. I [R, R1, R2, R3 = H, H, H, PhCMe2CH2 (HCl); H, Me, H, Me2CH (HCl); Et, H, H, PhCH2CH2 (HCl); H, H, H, cyclohexyl (HBr); H, Me, H, Me2CH (HCl); Et, Me2CHCO, H, Me2CH (HCl)] were prepared by reduction of II. I had immunosuppressive, antiallergic, and antiviral activities (no data). Thus, autoclaving a mixture of 1 g II.HCl (R = R1 = R2 = H, R3 = PhCMe2CH2), 0.2 g PtO2, 50 mL H2O, and 5 atm H at 80° for 20 h gave 0.8 g I.HCl (R = R1 = R2 = H, R3 = PhCMe2CH2).

RX(1) OF 2 A + B ===> C



RX(1) RCT A 15450-76-7, B 79-04-9
PRO C 56957-71-2

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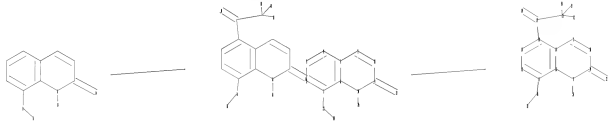

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ring nodes :
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28-32 36-37
ring bonds :
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exact/norm bonds :

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10-25  14-27  20-26  23-24  27-28  28-30  28-31  28-32  36-37
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6  11-12  11-16  12-13  13-14  14-15  15-16
isolated ring systems :
containing 1 : 11 :


Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom
11:Atom  12:Atom  13:Atom  14:Atom  15:Atom  16:Atom  17:Atom  18:Atom  19:Atom
20:Atom  21:CLASS  22:CLASS  23:CLASS  24:CLASS  25:CLASS  26:CLASS  27:CLASS
28:CLASS  29:CLASS  30:CLASS  31:CLASS  32:CLASS  36:CLASS  37:CLASS
fragments assigned product role:
containing 11
fragments assigned reactant/reagent role:
containing 1



L4      STRUCTURE UPLOADED

=> s l4 full
FULL SEARCH INITIATED 11:47:20 FILE 'CASREACT'
SCREENING COMPLETE -     3116 REACTIONS TO VERIFY FROM       92 DOCUMENTS

100.0% DONE    3116 VERIFIED       2 HIT RXNS                      2 DOCS
SEARCH TIME: 00.00.01

L5            2 SEA SSS FUL L4 (     2 REACTIONS)

=> d his

     (FILE 'HOME' ENTERED AT 11:42:10 ON 22 SEP 2008)

     FILE 'CASREACT, CHEMINFORMRX, DJSMONLINE, PS' ENTERED AT 11:42:27 ON 22
     SEP 2008
L1              STRUCTURE UPLOADED
L2            1 S L1
L3            7 S L1

     FILE 'STNGUIDE' ENTERED AT 11:46:18 ON 22 SEP 2008

     FILE 'CASREACT' ENTERED AT 11:46:52 ON 22 SEP 2008
L4              STRUCTURE UPLOADED
L5            2 S L4 FULL

=> s l5 and l3
L6            1 L5 AND L3

=> d l5 ibib abs rx 1-2


L5   ANSWER 1 OF 2  CASREACT  COPYRIGHT 2008 ACS on STN
```

ACCESSION NUMBER: 144:88180 CASREACT
TITLE: Method for preparing 8-substituted oxy-5-((R)-2-halo-1-hydroxy-ethyl)-(1H)-quinolin-2-ones employing a chiral reduction step
INVENTOR(S): Lohse, Olivier; Vogel, Caspar; Abel, Stephan
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis Pharma GmbH
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005123684	A2	20051229	WO 2005-EP6686	20050621
WO 2005123684	A3	20060601		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2005254698	A1	20051229	AU 2005-254698	20050621
CA 2566388	A1	20051229	CA 2005-2566388	20050621
CN 1968927	A	20070523	CN 2005-80019589	20050621
EP 1791820	A2	20070606	EP 2005-770221	20050621
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU				
JP 2008503526	T	20080207	JP 2007-517180	20050621
BR 2005012298	A	20080325	BR 2005-12298	20050621
IN 2006DN06563	A	20070831	IN 2006-DN6563	20061106
MX 2006PA14695	A	20070212	MX 2006-PA14695	20061214
KR 2007029752	A	20070314	KR 2006-726958	20061221
NO 2007000400	A	20070321	NO 2007-400	20070122
PRIORITY APPLN. INFO.:			GB 2004-13960	20040622
			WO 2005-EP6686	20050621

OTHER SOURCE(S): MARPAT 144:88180
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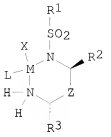
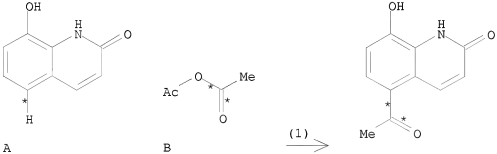


I

AB A process for preparing 8-substituted oxy-5-((R)-2-halo-1-hydroxy-ethyl)-(1 H)-quinolin-2-ones or acceptable solvates thereof which are useful intermediates from which to prepare 5-[(R)-2-(5,6-diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-(1H)-quinolin-2-one salts. The process involves reacting a 5-(α-haloacetyl)-8-substituted oxy-(1H)-quinolin-2-one with a reducing agent in the presence of a chiral agent and a base to form a 8-(substituted oxy)-5-((R)-2-halo-1-hydroxy-ethyl)-(1H)-quinolin-2-one, said chiral agent having a formula I [wherein M = Ru, Rh, Ir, Fe, Co, or Ni; L = aryl or arylalkyl; X = H or halo; R1 = alkyl, cycloalkyl, aryl, etc.; R2 and R3 = Ph or together form a cyclohexane or cyclopentane ring; Z = bond or 1,1'-ferrocenediyl].

RX(1) OF 73 A + B ===> C...



A B (1) C

YIELD 82%

RX(1) RCT A 15450-76-7

STAGE(1)
RGT D 7446-70-0 AlCl3
SOL 95-50-1 o-C6H4Cl2
CON 40 minutes, 20 - 25 deg C

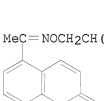
STAGE(2)
RCT B 108-24-7
SOL 95-50-1 o-C6H4Cl2
CON SUBSTAGE(1) 30 minutes, 20 deg C
SUBSTAGE(2) 30 minutes, 20 - 25 deg C
SUBSTAGE(3) 25 deg C -> 80 deg C

SUBSTAGE(4) 1 hour, 80 deg C

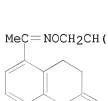
STAGE(3)
RGT E 7732-18-5 Water
CON SUBSTAGE(1) 80 deg C
SUBSTAGE(2) 15 minutes, reflux
SUBSTAGE(3) 15 minutes, 80 deg C

PRO C 62978-73-8
NTE regioselective, optimization study, optimized on stoichiometry

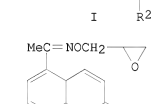
L5 ANSWER 2 OF 2 CASREACT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 102:6161 CASREACT
TITLE: Ether derivatives of oximes with a carbostyril ring. 4. Syntheses and β-blocking activities
AUTHOR(S): Amlaiky, Nourdine; Leclerc, Gerard; Decker, Nicole; Schwartz, Jean
CORPORATE SOURCE: Inst. Pharmacol. Med. Exp., Strasbourg, 67000, Fr.
SOURCE: European Journal of Medicinal Chemistry (1984), 19(4), 341-6
CODEN: EJMCA5; ISSN: 0223-5234
DOCUMENT TYPE: Journal
LANGUAGE: French
GI



I



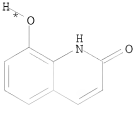
II



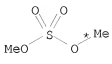
III

AB 5-Acetylcarbostyril oxime derivs. I and II [R = H, Me; R1 = CMe3, CHMe2, CHMeCH2Ph, 3,4-(MeO)2C6H3CH2CH2; R2 = OMe, OH, H], which were prepared, showed β-adrenergic blocking activity. A 5-acetylcarbostyril derivative was oximated, the oxime was treated with epibromohydrin, the ether product III was cleaved by Me3CNH2, and the I (R = H, R1 = CMe3, R2 = OCH2Ph) obtained was subjected to hydrogenolysis to give I (R = H, R1 = CMe3, R2 = OH).

RX(47) OF 89 COMPOSED OF RX(1), RX(2), RX(3)
RX(47) A + B + D ===> G



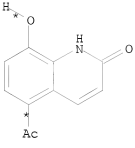
A



B

D

3 STEPS



G

RX(1) RCT A 15450-76-7, B 77-78-1
PRO C 22614-69-3

RX(2) RCT D 75-36-5, C 22614-69-3
RGT F 7446-70-0 AlCl3
PRO E 62978-76-1

RX(3) RCT E 62978-76-1
PRO G 62978-73-8
CAT 110-86-1 Pyridine, 628-13-7 Pyridinium chloride

=> d his

(FILE 'HOME' ENTERED AT 11:42:10 ON 22 SEP 2008)

FILE 'CASREACT, CHEMINFORMRX, DJSMONLINE, PS' ENTERED AT 11:42:27 ON 22 SEP 2008
L1 STRUCTURE UPLOADED
L2 1 S L1
L3 7 S L1

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     FILE 'STNGUIDE' ENTERED AT 11:46:18 ON 22 SEP 2008

     FILE 'CASREACT' ENTERED AT 11:46:52 ON 22 SEP 2008
L4              STRUCTURE UPLOADED
L5            2 S L4 FULL
L6            1 S L5 AND L3

=>

---Logging off of STN---


=>
Executing the logoff script...


=> LOG Y
TN INTERNATIONAL LOGOFF AT 11:51:23 ON 22 SEP 2008
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